Primary Vaccination of Indian Infants at 6, 10, 14 Weeks of Age with a Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, *Haemophilus Influenzae* Type B Conjugate Vaccine (Pentaxim)

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Background: Data on the immunogenicity and safety of acellular pertussis-based combination vaccines when given in the WHO recommended EPI schedule (6, 10 and 14 weeks of age) are needed for making individual clinical practice and public policy decisions in India.

Methods: This study assessed the immunogenicity and safety of primary vaccination at 6, 10 and 14 weeks of age with Pentaxim™ (sanofi pasteur, AcXim family vaccine) including diphtheria, tetanus, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b conjugate (PRP-T)antigens in 226 infants in India. Antibody titers were measured immediately before, and one month after, primary vaccination. Immunogenicity data from French infants vaccinated at 2, 3 and 4 months was used as a reference. Reactogenicity and safety were evaluated from parental reports.

Results: One month after the third dose, 90.0% of subjects had anti-PRP $\geq$ 1.0 μg/mL, and the GMT increased from 0.11 μg/mL to 4.17 μg/mL. Anti-Polio GMTs (1/dil U) increased from 18.1 to 441, from 20.4 to 459, and from 9.9 to 1511 for types 1, 2 and 3, respectively. Two-fold increase in PT and FHA antibody concentration occurred in 97.1% and 92.4% of subjects, and anti-PT and anti-FHA antibody titers $\geq$ 25 EU/mL were observed in 100% and 97.6% of children, respectively. The vaccine was well-tolerated, with low reactogenicity. Severe solicited reactions were documented in < 0.5% of subjects after any dose. No drop outs occurred because of adverse events.

Conclusion: Pentaxim given at 6, 10 and 14 weeks of age was well tolerated and induced large immune responses in Indian infants, similar to those observed in French infants vaccinated at 2, 3, 4 months of age in an earlier trial. [NCT00259337].

doi:10.1016/j.ijid.2008.05.433

21.020

Immunogenicity and Safety of Human Papillomavirus (HPV)-16/18 AS04 Adjuvanted Vaccine in Healthy Males Aged 10—18 Years

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Background: A human papillomavirus (HPV) 16/18 AS04 adjuvanted vaccine (*Cervarix*™, GlaxoSmithKline) has been 16/18 infections and associated precancerous lesions in 15—25 year-old women. Our study evaluated the immunogenicity and safety of *Cervarix*™ in 10—18 year-old healthy males.

Methods: This was a phase I/II, observer-blind, parallel-group study (580299/011/NCT00309166). Males were randomized (2:1 ratio) to receive *Cervarix*™ (n = 181) or hepatitis B vaccine (*Engerix-B*™, GlaxoSmithKline) (n = 89) at 0, 1 and 6 months and were followed for 7 months after the first dose.

Results: At Month 2, 100% of seronegative males in the HPV group had seroconverted for HPV-16 and 18 (ELISA) and remained seropositive at Month 7. At this time point, GMTs were respectively 4-fold and 2-fold higher, as compared to Month 2. The immune response to *Cervarix*™ in 10-18 year-old males was non-inferior for both seroconversion rates and GMTs to that seen in 15—25 year-old females in a previous study. The reactogenicity profile of the vaccine in males was similar to that reported in females. Compliance with 3-dose course was equally high (97%) in both groups.

Conclusion: *Cervarix*™ is immunogenic and well-tolerated in 10—18 year-old males, inducing anti-HPV-16 and 18 antibody responses non-inferior to those previously reported in 15—25 year-old females, among whom efficacy has been previously demonstrated. However, whether vaccination of adolescent males will ultimately prevent sexual transmission of oncogenic HPV types or have public health value remains to be determined.

doi:10.1016/j.ijid.2008.05.434

21.021

Modulation of Interleukin-18 Produces a Positive Impact on the Release of Proinflammatory and Antiinflammatory Cytokines During Malaria Infection

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Malaria infection is associated with the release of proinflammatory cytokines including TNF-alpha, IFN-gamma, IL-1, and IL-6. These cytokines play important roles in mediating the disease severity and involved in the pathogenesis and immunopathological reactions during the infection.

IL-18 is a potent pro-inflammatory cytokine and inducer of other cytokines release. In this study, we investigated the effect of modulating IL-18 production on the release of pro-inflammatory and anti-inflammatory cytokines (TNF-alpha, IFN-gamma, IL-1, IL-6 and IL-10) during malaria infection.

Plasmodium berghei infection in ICR mice was used as model for malaria infection. Mice were inoculated with parasitized red blood cells from donor mouse infected with *P. berghei*. Control animals received normal uninfected red blood cells. IL-18 production during the infection was modulated by treatment with the rIL-18, rIL-18 binding protein and anti-IL-18 monoclonal antibody. Blood samples for plasma were collected from the animals on day 1, 3 and 5 following inoculation and treatment. ELISA method

was employed to measure the levels of cytokines in the plasma.

IL-18 level in the plasma of malarial mice were found to be significantly elevated and positively correlated with the percentage degree of parasitaemia. Inhibition and neutralization of IL-18 production caused significant decrease in the plasma levels of pro-inflammatory cytokines TNF-alpha, IFN-gamma, IL-1 and IL-6. In contrast, the anti-inflammatory cytokine IL-10 was significantly increased. Treatment with rIL-18 on the other hand caused significant increase in pro-inflammatory cytokines plasma levels, whereas the anti-inflammatory cytokine level was significantly reduced.

Results proved the involvement of IL-18 in malaria infection. Its positive modulatory effects on the release of pro-inflammatory and anti-inflammatory cytokines during the infection may suggest its crucial role(s) in the pathogenesis of the infection. Results also suggest the IL-18 potential as an immunotherapeutic target in malaria therapy.

doi:10.1016/j.ijid.2008.05.435

21.022

Construction and Functional Evaluation of *rtx*C and *rtx*A/C Mutants of O139 *Vibrio cholerae*

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The diarrheal cholera is caused by *Vibrio cholerae* which colonizes the mucosal epithelium lining of small intestine and secretes cholera toxin (CT). Besides CT, several other accessory toxins like RTX, HA/protease also contributed to the reactogenicity of the disease. The RTX toxin is a multifunctional protein which causes rounding of host cells through Rho-GTPase inactivation and covalent cross-linking of actin. The toxin is encoded by *rtx*A gene which resides within RTX gene cluster, while *rtx*C gene codes for acyltransferase, activator for RTX toxin. Thus, the present study was carried out to mutate the *rtx*A/C gene in O139 *V. cholerae* and study virulence properties of the mutants. The colonization ability and fluid accumulation were done in animal models. While the effect of RTX toxin was tested by rounding assay using HEp-2 cell line. The formation of actin cross-linking to dimers, trimers and higher multimer were studied by Western blot analysis. The *rtx*A/C mutants were constructed by allele replacement method and were named as VCUSM9P (*rtx*C::*aph*A) and VCUSM10P (Δ*rtx*A/C). The mutations were confirmed by PCR and DNA sequencing. The RTX mutants colonized equally well in infant mouse as compared to the WT. Fluid accumulation elicited by RTX mutants were same as the WT but without haemorrhage. Rounding effect on HEp-2 cells was not observed in RTX mutants as compare with WT. But Western blot analysis showed that VCUSM9P still retained residual activity of RTX toxin, as actin multimer bands were detected. Actin multimer bands were not detected in VCUSM10P infected HEp-2 cells. Our finding shows that mutation of *rtx*C alone does not completely eliminate RTX toxicity, but mutation of *rtx*A and *rtx*C gene completely eliminate RTX toxicity. In conclusion, we have constructed an O139 RTX mutant strains which has good colonizing ability though it is reactogenic due to the presence of intact ctx operon.

doi:10.1016/j.ijid.2008.05.436

21.023

Hepatitis C Virus Infection Protein Network

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Replication of Hepatitis C virus (HCV) relies on multiple interactions with host factors but how these interactions determine infection, sensitivity to treatment and pathogenesis remain largely undefined. In a first attempt to provide a comprehensive view of a cellular infection by HCV, we present here a proteome-wide mapping of interactions between HCV and human cellular proteins. This interaction map was first generated by stringent high-throughput yeast two-hybrid (Y2H) screening, using both full-length HCV proteins and domains as baits. This map was then completed by an extensive mining of the literature. A total of 314 pairwise interactions between HCV and human proteins was identified by Y2H, and 170 by literature mining. The entire dataset was integrated into a reconstructed human interactome composed of 9,520 proteins and 44,223 interactions. The topological analysis of this network indicated that cellular proteins interacting with HCV are enriched in highly central and interconnected proteins, suggesting that HCV preferentially targets proteins with essential functions. A global analysis of these proteins based on functional annotation showed a highly significant enrichment for cellular pathways related to pathogenesis. A network comprising proteins associated to frequent clinical disorders of chronically infected patients was constructed by connecting the insulin, Jak/STAT and TGF-beta pathways with cellular proteins targeted by HCV. CORE protein appeared as a major perturbator of this network. The focal adhesion was also identified as a new function affected by the virus, mainly by NS3 and NS5A proteins.

doi:10.1016/j.ijid.2008.05.437

21.024

Identification of *Candida tropicalis* Immunoreactive Proteins by Immunoproteomics

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Candida tropicalis is the most commonly isolated species found in systemic candidiasis and could have greater virulence than other *Candida* species. The transition from a commensal to a pathogen may be due to its ability to change its cellular morphology, adhesion factors, phenotypic switching and extracellular proteolytic activity. Thus, to further elucidate the involvement of *Candida tropicalis* proteins in pathogenesis, we generated systemic candidia-